

SYSTEMIC CANDIDIASIS AND ENDOCARDITIS DUE TO *C. TROPICALIS*

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[WITH SPECIAL PLATE]

Mucocutaneous candidiasis is a well-recognized complication of severe debilitating illness, and has become more common since the widespread use of antibiotics. It may precede systemic candidiasis, which sometimes manifests itself as a septicaemic illness with endocarditis. The following case is reported to emphasize the gravity of this complication and to record an endocardial lesion of unusual nature.

Case Report

Clinical History

The patient was a woman of 61 who had suffered from dyspepsia for 20 years. Symptoms had been severe for the last 12 months, and on admission to hospital she was grossly undernourished, weighing only 91 lb. (41.277 kg.), and had marked epigastric tenderness. Chronic rheumatoid arthritis affected the fingers, wrists, elbows, shoulders, and knees. A barium-meal examination showed scarring of the duodenal cap and a large gastric ulcer. Urine analysis was normal. Erythrocyte sedimentation rate (E.S.R.) 50 mm. in the first hour (Westergren); erythrocytes 4,400,000 per c.mm.; haemoglobin 9.6 g. per 100 ml.; P.C.V. 31%; total and differential white counts normal; plasma albumin 2.3 g. and globulin 2.9 g. per 100 ml.; blood urea nitrogen 11 mg. per 100 ml.

A modified Schoemaker type Billroth I gastrectomy was performed on June 6, 1957, for a simple gastric ulcer. Fifteen days later she was discharged well, weighing 90 lb. (40.82 kg.). Within two days fever with rigors and vomiting developed, and she was readmitted on July 11. She weighed 85 lb. (38.56 kg.) and looked ill, but no new abnormality was found. Urine analysis on four occasions was normal. W.B.C. 4,600 per c.mm. (neutrophils 57.5%, lymphocytes 33%, monocytes 7.5%, eosinophils 2.0%); E.S.R. 20 mm. in one hour; haemoglobin 13 g. per 100 ml. Radiographs of chest and infradiaphragmatic areas were normal. The fever persisted until July 13 (see Chart). She left hospital against advice on July 15, but had to be readmitted on the 19th because the rigors and vomiting recurred. She looked ill, her temperature was 103° F. (39.4° C.), and her urine contained numerous pus cells. W.B.C. 12,000 per c.mm., E.S.R. 42 mm. in one hour, haemoglobin 15 g. per 100 ml., P.C.V. 48%; serum electrolytes normal; blood urea nitrogen 17 mg. per 100 ml. Rehydrating intravenous infusion was maintained for 72 hours, and 1 g. streptomycin and 1 mega unit of penicillin per day were administered for seven days. The fever resolved and her general condition improved. Vomiting persisted, however, for the following four weeks, and a laparotomy was performed on August 16. The stoma was found to be narrowed by a plaque of fibrous tissue projecting into the lumen, and the obstruction was successfully relieved. There was no evidence of intra-abdominal sepsis.

Throughout the time from her admission on July 19 until her death 57 days later pus cells were constantly found in

the urine, and *Escherichia coli*, *Proteus vulgaris*, and *Pseudomonas pyocyanea* were cultured on five different occasions from catheter specimens (see Chart). During this time she received a total of 28 g. streptomycin, 28 mega units of penicillin, 24 g. sulphadimidine, and 8 g. terramycin, each drug being prescribed according to the sensitivities of the urinary organisms.

High fever and rigors recurred on August 26, and thereafter her condition deteriorated. By now arthralgia, inanition, and anorexia were severe, and her body weight had fallen to 78 lb. (35.38 kg.). Because the arthralgia was resistant to analgesics she was given 37.5 mg. cortisone daily (total 525 mg.) from August 31 until her death 14½ days later. Intravenous infusion was maintained through a polythene catheter introduced into the inferior vena cava. Each day at least 2 litres of 20% glucose, 80 ml. absolute alcohol, and various electrolytes were administered by this route.

In the last seven days of her life she developed uraemia manifested by deepening coma and twitchings, rising blood urea nitrogen (from 10 mg. to 150 mg. per 100 ml.), acidosis (carbon-dioxide-combining power 9 mEq per litre), and hyponatraemia (serum Na 113 mEq per litre).

Blood cultures on September 8, 10, and 14 yielded growths of *Candida tropicalis*. On September 12 a throat swab, a vulvar swab, and a urine specimen were taken, and on culture each yielded growths of *C. tropicalis*. There was no clinical evidence of mucocutaneous candidiasis at this or any other time. She died on September 15.

Necropsy Findings

Necropsy was performed four hours after death. The abdominal wounds were soundly healed. The legs were oedematous. There were no obvious candida lesions of the mucosa of the alimentary or respiratory tracts or of the vagina. The stomach was in satisfactory post-operative condition, and no inflammatory changes were obvious in its wall. There was, however, a small quantity of organizing fibrino-purulent exudate between the anterior wall of the stomach and the under surface of the left lobe of the liver. The kidneys were about twice their normal size, and numerous yellow abscesses, measuring about 1 mm. in diameter, were present on their subcapsular and cut surfaces. The cortex was swollen and pale, the medulla was streaked by the linear abscesses of acute pyelonephritis, and the mucosa of the calices and pelves was inflamed. The mucosa of the urinary bladder showed marked inflammatory oedema without membrane formation. The heart was dilated. The valve cusps were normal, but on the right atrial endocardium large, flat, yellow-grey vegetations which were firm and fairly smooth extended from the entrance of the inferior vena cava towards the superior vena cava and thence anteriorly on to the adjoining trabeculae (Special Plate, Fig. 1). On the subaortic endocardium of the left ventricle there were several small, flat, circular vegetations which appeared to cover minute myocardial abscesses. On the intima of the trunk of the pulmonary artery were several pale vegetations, measuring about 1 mm. in diameter, resembling colonies on a culture plate. The liver was swollen, soft, and congested. The lungs showed only basal congestion and slight oedema. The spleen weighed 300 g. and was congested. Direct smears from the kidneys, the right atrial vegetation (Special Plate, Fig. 2), and the exudate between the stomach and liver contained numerous candida-like organisms. The kidney smears also contained coccal and bacillary organisms. *C. tropicalis* was isolated from the peritoneal exudate and the kidney surface.

Microscopical Examination

In the stomach the anastomosis was soundly healed and there was no evidence of intramural candida infection. The kidneys showed severe acute pyelonephritis with a predominantly polymorphonuclear inflammatory exudate; numerous yeast-like organisms were present in the tubules and in the small abscesses (Special Plate, Fig. 3). In the

heart the vegetation on the right atrium consisted mainly of laminated thrombus. The atrial myocardium did not appear to be infected, and the reaction in the affected portion of endocardium was mild. Colonies of yeast-like organisms were present on the surface of the vegetation (Special Plate, Fig. 4). The vegetations in the pulmonary artery were composed almost entirely of surface colonies of similar organisms (Special Plate, Fig. 5). Sections of the ventricular myocardium contained a few widely separated minute polymorphonuclear abscesses. Other organs showed toxic and congestive changes without evidence of infection.

Identification of *Candida*

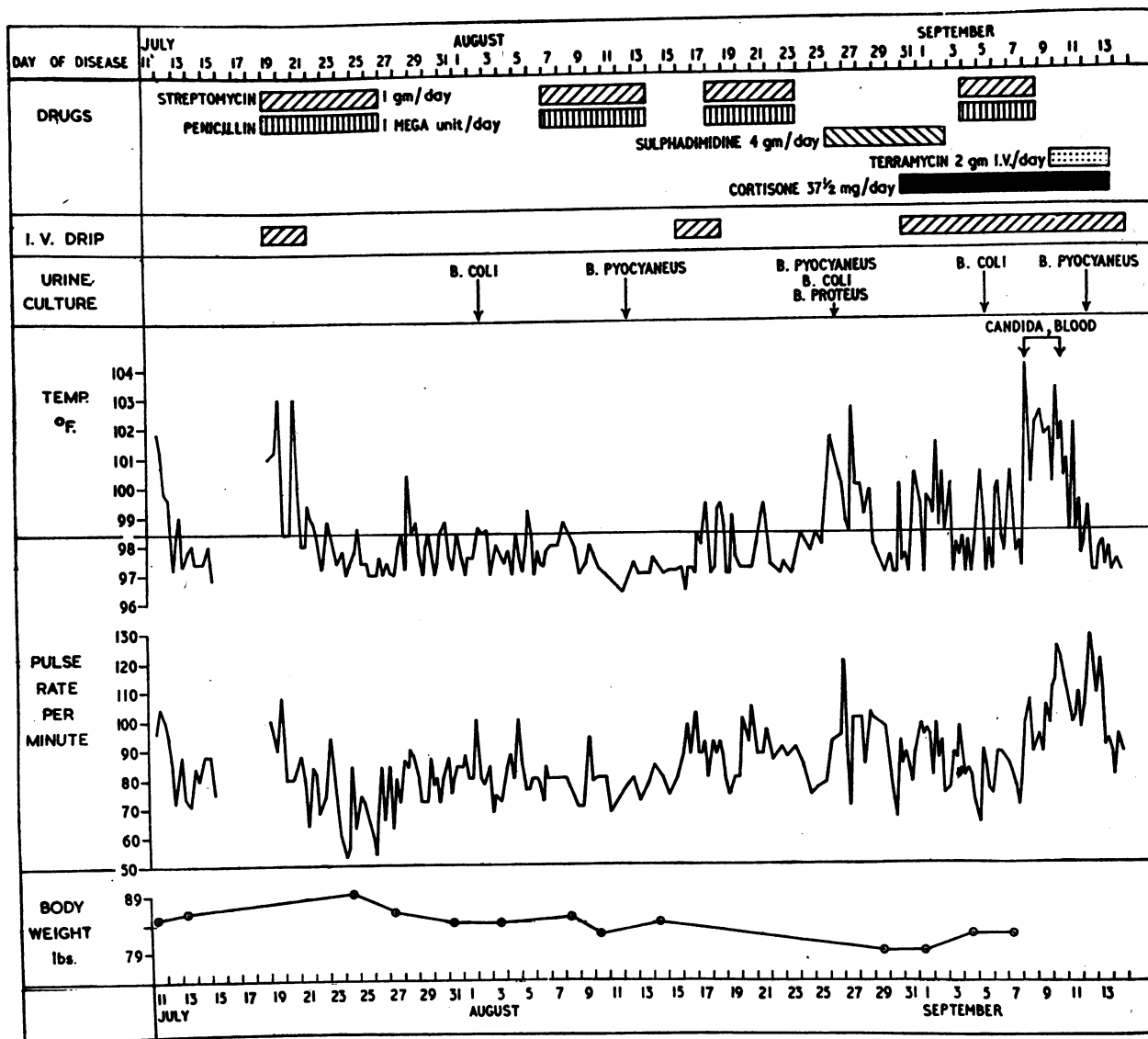
After 24 hours' incubation at 37° C. colonies were visible in all three blood-culture bottles, both on the surface and suspended throughout the broth; they were yellow, globular, and were ill-defined at their margins (Special Plate, Fig. 6). Stained films of these colonies revealed oval yeast-like cells. Sub-cultures on Sabouraud's glucose agar medium and corn-meal agar were incubated at 25° C. The inoculating wire was cut into the surface of the corn-meal agar medium. Specimens of urine and urethral discharge, and from the throat, and post-mortem specimens from kidney and peritoneum, were also inoculated on to similar media and incubated at 25° C. Within 24-48 hours colonies appeared

on Sabouraud's medium which were smooth, matt, of creamy colour and granular consistency, and with a slight grittiness noted on manipulation with an inoculating wire, not found in typical colonies of *C. albicans*. The colonies had a distinct yeasty odour. Macroscopically, the colony on corn-meal agar appeared similar to that of *C. albicans*. Repeated microscopical examination revealed mycelium, pseudo-mycelium, blastospores, but no chlamydospores.

Biochemical tests gave the following reactions: glucose—acid and gas; lactose—nil; sucrose—acid and gas; maltose—acid and gas. The colony characteristics and biochemical reactions were identical in cultures from the blood, throat, urine, urethral discharge, and post-mortem specimens of kidney and peritoneum.

The identification of the *Candida* as *C. tropicalis* was confirmed by using the criteria laid down by Lodder and Kreger-Van Rij (1952), which included the use of malt extract, malt agar, and corn-meal agar media, also carbohydrate fermentation and carbohydrate and nitrate assimilation tests.

Mice of strains A., C.B.A., and University of Birmingham were inoculated with pure cultures (approximately 2,000,000 blastospores per 0.2 ml.). The cultures were pathogenic for all three strains, in particular strain A., in which bilateral renal involvement was severe.



GASTRECTOMY 6-6-57, DISCHARGED 21-6-57, 15TH POST-OPERATIVE DAY.

Chart showing course of illness, cultural findings, and treatment.

Discussion

Species of *Candida* can be isolated from the skin and mucous membranes of healthy individuals so frequently that it is often difficult to assess the significance of a single positive culture. For example, Dawkins *et al.* (1953) isolated such species as *C. albicans*, *C. krusei*, *C. parakrusei*, *C. tropicalis*, and *C. mycoderma* from the vagina in 57 of 500 healthy women. If, however, the fungus is isolated consistently, and from many different sites simultaneously, a diagnosis of candidiasis may be warranted.

Systemic candidiasis or moniliasis is a grave disease which may manifest itself as a generalized mucocutaneous eruption, as bronchopulmonary inflammation, or as a septicæmic illness. The kidneys, meninges, or bone may be isolated sites of deep candida infection, and the endocardium may also be involved. Monilial (candida) endocarditis was first reported in drug addicts habituated to self-administration of heroin or opium, but more recently it has been encountered in patients receiving antibiotic therapy (see Table). The valvular endocardium is principally attacked. Of 12 cases examined, post mortem vegetations were found on the mitral valve in six, on the aortic valve in three, and on both aortic and mitral valves in three: in eight cases the affected valves were thickened by fibrosis from previous disease. There were certain similarities between the disease in these patients and subacute bacterial endocarditis—the vegetations were usually large, and embolic phenomena such as systemic infarcts, focal embolic nephritis, and mycotic aneurysms were common. By analogy, therefore, the disease might be termed subacute monilial endocarditis. In this condition the less pathogenic members of the *Candida* species, such as *C. guilliermondi* and *C. parakrusei*, seem to be able to infect valves already damaged by disease (see Table).

The endocarditis in our patient differed from the reported cases of monilial endocarditis (1) in the species of infecting organism, (2) in the situation of the cardiac lesions, and (3) in the nature of the infective process. There have been no previous reports of endocarditis caused by *C. tropicalis*, although this organism has been isolated in a case of septicæmic candidiasis (Brown *et al.*, 1953), in osteomyelitis (Weingart *et al.*, 1942), and in broncho-pulmonary disease (Duroux *et al.*, 1954). The site of the endocarditis was also unique: the valves were unaffected, and the only large vegetations were in the right atrium where the blood entering from the inferior vena cava impinged upon the endocardium. Vegetations of the type present in the pulmonary artery have not been described previously: they probably

resulted from surface infection by *C. tropicalis* carried in the stream of blood leaving the right ventricle. On the other hand, the small vegetations in the subaortic area of the left ventricle, although superficially similar, appear to have formed on the endocardium overlying small monilial abscesses in the myocardium. Lastly, the presence of abscesses in the myocardium and in the kidneys indicated that the infection was septicæmic. In this respect our case resembles Wolfe and Henderson's (1951) case and that of Kunstadter *et al.* (1952), and those cases, without endocarditis, in which *C. albicans* was the usual infecting organism (Duhig and Mead, 1951; Gausewitz *et al.*, 1951; Brown *et al.*, 1953; Schaberg *et al.*, 1955; Zimmerman, 1955; Matthias and Rees, 1956; and Barrett *et al.*, 1957).

It is not necessary to postulate that the severity of the renal lesions was conditioned by a previous bacterial infection, since monilial abscesses are most numerous in the kidneys in both experimental and clinical septicæmic candidiasis. *C. tropicalis*, however, was not isolated from the urine until a late stage of the illness, despite repeated cultures on a medium known to promote the growth of *Candida*. This suggests that, like the tubercle bacillus, the organism may escape less readily to the lower urinary tract than do coliform bacilli and other motile organisms. The urinary bacterial infection proved to be clinically misleading, since the continued pyrexia was attributed to bacterial pyelonephritis. It now seems probable that the cause of the pyrexia was, in fact, an unsuspected monilial infection.

In most recorded cases of subacute monilial endocarditis antibiotics either had not been administered, or had been given during an established infection which proved to be monilial. In contrast, antibiotic therapy has preceded monilial infection in most cases of septicæmic candidiasis, and, although severe candida infection is only likely to occur in debilitated subjects, there can be little doubt that prolonged administration of antibiotics increases the risk of this complication. Antibiotics have a similar action in rabbits infected by *C. albicans* var. *stellatoidea* (Foley and Winter, 1949), but they do not appear to potentiate growth *in vitro* of *Candida* (Woods *et al.*, 1951). They probably act by suppressing bacterial flora, reducing competition for nutritional factors, and thus indirectly enhancing monilial growth. Induced deficiency of vitamin-B complex has been advanced to explain their action (Harris, 1950), but Meenan (1957) concluded that vitamin-B administration did not influence the incidence of *C. albicans* infection in patients receiving antibiotic therapy.

Table Showing Details of Reported Cases of *Candida* (Monilial) Endocarditis

Authors	Patient's Age and Sex	Drug Addiction	Ætiological Importance of Antibiotics	Infecting Organism	Valves Affected	Valvular Fibrosis	Systemic Infarcts	Focal Embolic Nephritis	Probable Classification of Endocarditis
Joachim and Polayes (1940)	M 48	Heroin	Nil	<i>C. parakrusei</i>	Aortic		+		Subacute monilial endocarditis
Wikler <i>et al.</i> (1942)	M 49	"	"	"	Mitral	+			" " "
Helpern and Weiner	"	"	"	"	"				" " "
Peery	"	"	"	<i>C. guilliermondi</i>	"				" " "
Luttgens (1949)	M 32	Opium	"	No culture	Aortic and mitral				" " "
Zimmerman (1950)	F 38	Heroin	"	<i>C. guilliermondi</i>	Mitral	+	+		" " "
Pasternack (1942)	M 45	No	"	<i>C. parakrusei</i>	Aortic	+	+	+	" " "
Wolfe and Henderson (1951)	F 57	"	Doubtful	<i>C. krusei</i>	Mitral				Septicæmic endocarditis
Kunstadter <i>et al.</i> (1952)	M 7/12	"	Unlikely	<i>C. albicans</i>	"				" " "
Kohlmeier (1953)	M 41	"	Doubtful	"	Aortic and mitral	+		+	Subacute monilial endocarditis
Niel (1953)	F 60	"	Nil	<i>C. guilliermondi</i>	"	+	+	+	" " "
Koelle and Pastor (1956)	M 40	"	Doubtful	<i>C. albicans</i>	Aortic	+	+		" " "
Geiger <i>et al.</i> (1946)	F 19	"	Probable	"	Mitral	+	+		" " "
Caplan (1955)	M 43	"	"	No culture	"	+	+	+	" " "
Present authors	F 61	"	"	<i>C. tropicalis</i>	R. atrial endocardium				Septicæmic endocarditis

In the present patient extreme debility and prolonged antibiotic therapy were probably the most important factors in the development of systemic candidiasis. Latterly the progress of the disease may have been accelerated by cortisone therapy and by intravenous administration of 20% glucose saline. Indeed, Duhig and Mead (1951) and Schaberg and his colleagues regarded the prolonged use of intravenous glucose saline as an important factor in establishing the infection in their cases. Some form of injection appears to be common to all cases of systemic candidiasis irrespective of the use of antibiotics. Here, however, infection from the alimentary tract may have occurred at operation, since local peritoneal exudate infected with *C. tropicalis* was present between the stomach and liver at necropsy. Systemic candidiasis has been reported after duodenal perforation or abdominal operations on a number of occasions (Brown *et al.*; Schaberg *et al.*; Caplan, 1955; Matthias and Rees; Barrett *et al.*).

This case illustrates the various clinical factors predisposing to the development of systemic candidiasis. The history suggests that *Candida* may proliferate in the blood of a patient without any clinical signs of systemic moniliasis appearing other than pyrexia. Unexplained pyrexia occurring in prolonged debilitating diseases, especially where antibiotics and intravenous alimentation have been used, is an indication for culturing the blood in media suitable for the growth of fungi.

Summary

A case of systemic candidiasis due to *C. tropicalis* infection is recorded, and the clinical features, bacteriological investigations, and pathological findings are described. *C. tropicalis* endocarditis affected the right atrium. Other cases of monilial endocarditis are reviewed, and the aetiology and pathogenesis of the condition are discussed.

We thank Dr. W. Circus for permission to publish this case, and are indebted to Dr. W. Blyth and Mr. D. W. R. Mackenzie, of the Experimental Mycosis Unit, Department of Botany, Edinburgh University, for confirmation of the *Candida* species.

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INDUCTION OF SARCOMA IN THE RAT BY IRON-DEXTRAN COMPLEX

BY

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[WITH SPECIAL PLATE]

Pathological amounts of iron may accumulate in the body in a variety of conditions—for example, haemochromatosis and transfusional, malnutritional, and occupational siderosis. In all these conditions arguments for and against the cytotoxic effects of iron have been advanced, but the possibility that this metal plays any part in carcinogenesis has hardly been entertained. Therefore, in the belief that iron was non-carcinogenic if not altogether bland, an iron-dextran complex ("imferon," Bengel Laboratories Ltd.) was deliberately chosen in order to establish a progressive mobilization or "hyperplasia" of histiocytes. This need arose when it had been discovered (Richmond, unpublished observation) that repeated subcutaneous injections of trypan blue commonly induced a pleomorphic histiocytic sarcoma in the rat at the site of injection. By a collateral series of experiments with a non-carcinogenic substance it was hoped to detect some critical difference between a "hyperplasia" and a neoplasia of histiocytes. This hope was not realized because another crop of pleomorphic histiocytic sarcomas histologically identical with those induced by trypan blue was obtained as detailed below.

All the rats belonged to a home-bred hooded strain in which no spontaneous tumours of this kind have previously been recognized in this laboratory. They were fed on Diet No. 1 (Thomson cube) supplemented with greens.

Experimental Procedures

Experiment 1.—The animals were all adult males within the weight range of 250–300 g. at the beginning of the experiment. (a) 40 received a weekly intramuscular injection of 0.4 ml. iron-dextran complex into the right upper thigh. Each dose contained 20 mg. of iron as ferric hydroxide in complex with low-molecular-weight dextran. (b) 12 received weekly intramuscular injections of 0.5 ml. "ferrivenin" (Benger) under ether anaesthesia, with occasional interruptions owing to the development of ulceration. Each dose contained 10 mg. of iron as saccharated oxide of iron. (c) 12 received weekly injections of 0.5 ml. low-molecular-weight dextran. (d) 12 received weekly injections of 0.5 ml. normal saline solution.

Experiment 2.—The animals were weanling rats of both sexes averaging 48 g. in weight. (a) 20 males and 20 females were given twice-weekly intramuscular injections of iron-dextran complex into the right upper thigh in graduated dosage according to weight—namely, 0.1 ml. up to 100 g., 0.2 ml. up to 150 g., 0.3 ml. up to 200 g., and 0.4 ml. thereafter. This regimen was stopped after three months, each animal

M. A. BIRNSTINGL: SURGICAL DIAGNOSIS OF "CHRONIC PANCREATITIS"



FIG. 3.—Extensive calcification in pancreas of woman aged 24 with chronic relapsing pancreatitis.



FIG. 4.—Barium-meal radiograph of male aged 31 with chronic relapsing pancreatitis, showing distortion of upper part of duodenum by pancreatic cyst and scattered pancreatic calcification.

NANCY K. CONN *ET AL.*: SYSTEMIC CANDIDIASIS DUE TO *C. TROPICALIS*

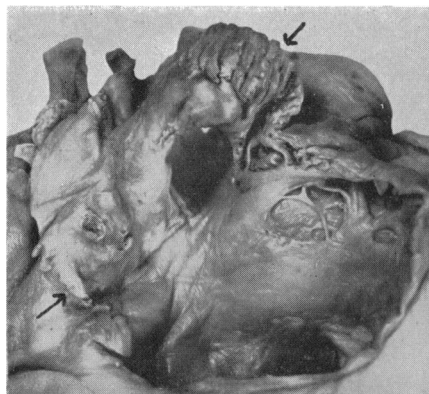


FIG. 1.—In right atrium vegetations extend from entrance of inferior vena cava (arrow bottom left), upwards around orifice of superior vena cava, and onwards to adjoining trabeculae (arrow top right).

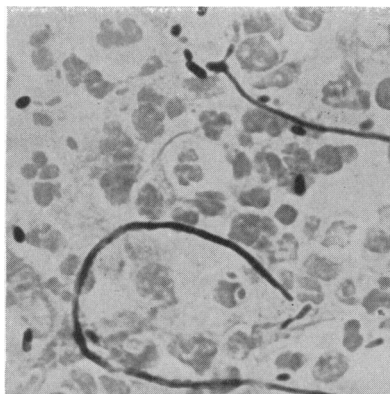


FIG. 2.—Direct smear from right atrial vegetation, showing *C. tropicalis* as mycelium and oval yeast-like cells. (Gram. $\times 618$.)

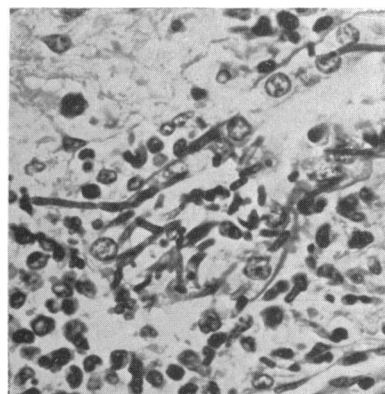


FIG. 3.—Renal collecting tubule containing *C. tropicalis* and surrounded by acute inflammatory exudate. (P.A.S. (McManus). $\times 500$.)

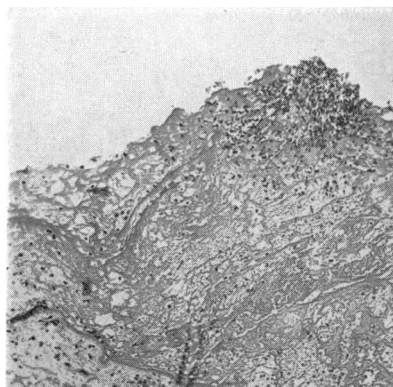


FIG. 4.—Portion of vegetation in right atrium showing colony of *C. tropicalis* surmounting laminated thrombus. (H. and E. $\times 100$.)

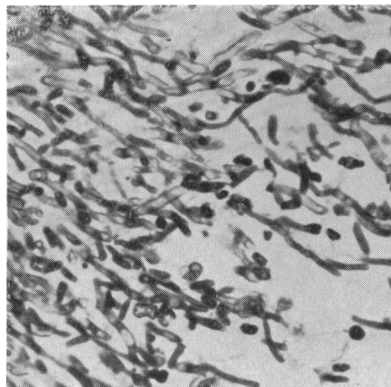


FIG. 5.—Portion of one of small vegetations on pulmonary artery consisting of *C. tropicalis* as mycelium and oval yeast-like cells. (P.A.S. (McManus). $\times 500$.)

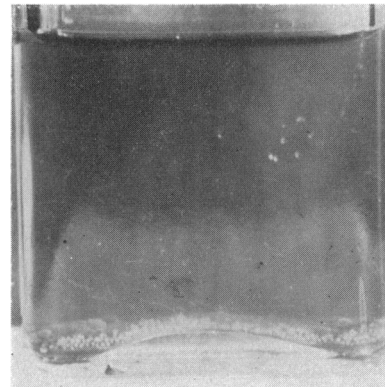


FIG. 6.—Glucose broth blood culture after 24 hours' incubation at 37° C., showing colonies of *C. tropicalis* deposited at base of bottle.